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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,870	08/06/2001	Bernhard Palsson	PALSSN.002C1	1729

7590 12/22/2006

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/923,870	PALSSON, BERNHARD	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-54,56-62,64 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-54, 56-62, 64-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 9/29/06 have been fully considered but they are not persuasive. In addition, new ground(s) of rejection are set forth below. This action is being made non-final as not all of the new rejections are due to applicant's amendments.

Claims 49-54, 56-62, and 64-65 are under consideration by the examiner.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant is reminded that no agreement was reached with respect to the claims at the interview held on 8/22/06. There were no written proposed claim amendments presented to the examiner prior to or during this interview.

Claim Objections

Claims 53-54 are objected to because of the following informalities: the claims contain a typographical error, "silco." Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 49-54, 56-62, and 64-65 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a various methods or processes. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims,

there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result. In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. In the instant case, the claims do not produce a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. In the method as claimed, the method is performed in a computer but does not require that the result be output, saved, or displayed in a tangible form. In claims 53, 56-62, and 64-65, it is unclear what tangible result is the *in silico* representation. It is clearly something beyond the stoichiometric matrix of claim 49 but the claim does not make clear what form it takes. Is it a computer readable file, a series of equations, a value? What information would be output, saved, or displayed? Finally, the last step of claim 54 is performing a flux balance analysis on said *in silico* representation. It is unclear what the useful, concrete, and tangible result of this method is once the flux balance analysis is performed. Is it a value or a conclusion about the representation or something else? What information would be output, saved, or displayed?

Claim Rejections - 35 USC § 112

Claims 49-54, 56-62, and 64-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 49 has been amended to recite "a number of DNA sequences in a genome sufficient to produce an *in silico* representation of a microbe." Claim 57 has been amended similarly. Applicant has pointed to various pages of the specification for support. This is not agreed with. The specification discloses "most of all of the metabolic reactions," "most or all of the genes," and "nearly the entire gene complement." However, the claims as amended do not reflect these concepts and embrace new matter. There is no disclosure on what number of sequences would be "sufficient to produce an *in silico* representation" nor any disclosure as to how one of ordinary skill in the art would know when a sufficient number had been reached. The claims embrace less than "most" or "nearly all" of the genes unless this is the number required to be sufficient. However, this is not known or disclosed. Applicant's originally filed specification does not reasonably convey to one of ordinary skill in the art that the invention as presently claimed was contemplated.

Claim 54 has been amended to be directed to a method of simulating a metabolic capability of an *in silico* representation of a microbe. Claim 65 has been amended similarly. Applicant has pointed to portions of the specification including page 13 for support. This is not agreed with. Page 13 discloses metabolic capabilities and simulations.

> "Thus, by adding or removing constraints on various fluxes in the network it is possible to (1) simulate a genetic deletion event and (2) simulate or accurately provide the network with the metabolic resources present in its in vivo environment. Using flux balance analysis it is possible to determine the affects of the removal or addition of particular genes and their associated reactions to the composition of the metabolic genotype on the range of possible metabolic phenotypes. If the removal/deletion does not allow the metabolic network to produce necessary precursors for growth, and the cell cannot obtain these precursors from its environment, the deletion(s) has the potential as an antimicrobial drug target. Thus by adjusting the constraints and defining the objective function we can explore the capabilities of the metabolic genotype using linear programming to optimize the flux distribution through the metabolic network. This creates what

> we will refer to as an in silico bacterial strain capable of being studied and manipulated to analyze, interpret, and predict the genotype-phenotype relationship."

Adding or removing constraints and/or adding or removing particular genes to determine effects are not present in the methods of claims 54 and 65. There are no manipulative steps recited and these appear to be required by the disclosure for simulating or exploring the capabilities of the metabolic genotype.

It is further noted that the final step in claim 54 is performing a flux balance analysis. However, this step is omitted from claim 65. In fact, claim 65 appears to have a different preamble or intended goal than claim 61 but exactly the same steps. Based on its dependency on claim 61, claim 65 appears to be directed to a method where the steps of producing the *in silico* representation are repeated. There does not appear to be any basis for this.

Claim 53 remains new matter for reasons of record. Contrary to applicant's arguments, claim 53 as written does not require or recite formulating the general linear programming problem representing the *in silico* strain of the organism (step 64 in Figure 2). The concept set forth in step 64 is not synonymous with combining the metabolic demands and uptake rates with the stoichiometric matrix as recited in claim 53. Likewise, claim 54 as written does not require or recite solving the general linear programming problem by, for example, using flux balance analysis. Applicant's originally filed specification does not reasonably convey to one of ordinary skill in the art that the invention as presently claimed was contemplated.

Claims 49-54, 56-62, and 64-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

The specification does not provide guidance on what number of sequences would be "sufficient to produce an *in silico* representation" nor any disclosure as to how one of ordinary skill in the art would know when a sufficient number had been reached. There do not appear to be any objective criteria disclosed in the specification by which a determination of a sufficient or insufficient number could have been evaluated. As such, these methods are not enabled.

Claim 65 appears to be incomplete and the steps as recited would not result in the intended goal of the preamble. As such, this method is not enabled.

Claim Rejections - 35 USC § 102

Claims 49-51, 53-54, 56-59, 61-62, and 64-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Schilling et al. (Biotech. Prog., 15(3):288-295, May/June 1999, of record).

This rejection is maintained for reasons of record. As the claims as presently written embrace new matter, applicant is entitled to only the instant filing date of 8/6/01 and not the filing date of parent application 09/243,022.

Claim Rejections - 35 USC § 103

Claims 52 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schilling et al. al. (Biotech. Prog., 15(3):288-295, May/June 1999, of record).

This rejection is maintained for reasons of record. Schilling remains valid prior art.

Claims 49-54, 56-62, and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Blattner et al. (Science, 1997, of record), Pennisi (Science, 1997), Edwards et al. (Abstracts of Papers, American Chemical Society, 213(1-3):BIOT 50, San Francisco, April 13-17, 1997), and Pramanik et al. (Biotechnology and Bioengineering, 1997, of record).

This rejection is maintained for reasons of record.

Applicant continues to argue that Pramanik et al. teaches away from using models that are not produced from existing biochemical information. This is not agreed with. Page 4 of the specification discusses Pramanik et al. However, these concerns are not applicable with respect to the art applied as biochemical information was known at the time of the invention for the organisms suggested.

Again, Edwards et al. discloses flux balance analysis of a metabolic network for *H. influenzae* based on homology of putative proteins with those encoded by the known part of the *E. coli* genome. Thus, the information is rooted in known biochemical information. Blattner, Pennisi, and Pramanik et al. establish that *E. coli* and *H. influenzae* biochemical information would have been well known at the time of the invention. In addition, the response by applicant clearly argues that collecting pertinent information from all available sources is intended to enable and perform the claimed method.

It is maintained that it would have been obvious to produce a stoichiometric matrix and *in silico* model of the microbes *E. coli* and *H. influenzae* according to Pramanik et al. using the known genome sequence, ORFs, and metabolic genes for these microbes as disclosed by Blattner et al. and Pennisi et al. (where function has been assigned by using homology and tools such as

BLAST). Such models clearly would have been of interest and within the skill of the art to produce as seen by Edwards et al. One would have been motivated to produce the stoichiometric matrix and *in silico* model in order to better understand microbial metabolism and provide more robust models of metabolism. The art applied is analogous and looks to further characterize the same microbial metabolic systems. It is maintained that it would have been obvious to combine the teachings of the prior art in order to arrive at the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marianne P. Allen

Marianne P. Allen

12/19/06

Primary Examiner
Art Unit 1647

mpa